

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Michel VAULTIER et al.

Conf. 4777

Application No. 10/529,361

Group 1793

Filed November 3, 2005

Examiner C. Koslow

COMPOSITIONS CONTAINING IONIC LIQUIDS
AND THEIR USES, IN PARTICULAR IN ORGANIC SYNTHESIS

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, LEMAIRE Marc declare as follows:

I am a Professor at Lyon 1 University. My relevant background and experience are set forth on the attached CV.

I have read the Official Action mailed April 4, 2008 that rejects the claimed invention as being obvious over US patent application publication 2002/0010291, and I am familiar with the present application.

The compositions according to the claimed invention are not suggested by the composition described in US patent application publication 2002/0010291. In particular, there is no recognition of (1) a recyclable composition or (2) a soluble reaction support. The claimed invention satisfies a long-felt need by utilizing a composition that includes both (1) a recycle composition and (2) a soluble reaction support for organic synthesis.

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Synthesis on a solid support has become a very effective method often used for the production of combinatorial libraries of products (Wilson et al., 1997; Charken et al., 1996; Sammelson et al., 2001; Gravet et al., 1997; Wentworth et al., 1999). Such combinatorial libraries have become very important in pharmaceutical chemistry and in agricultural chemistry.

The use of suitably functionalized Merrifield resins, for example, has made it possible to develop a multitude of methodologies for synthesis on solid support (Thompson et al., 1996; Dörwald, 2000).

However, the resin solid-support methodologies have numerous disadvantages.

For example, the reactions take place in a heterogeneous phase, which requires a particular development in each case, the reaction conditions being generally different from those used in solution. Moreover, it is difficult to use high-temperature reactions, magnetic or mechanical stirring, during the release of the desired products, as these conditions destroy the solid supports.

The use of soluble polymers (Sammelson et al., 2001; Gravet et al., 1997) proved to be a useful alternative to resin solid-supports. In fact, the substitution of insoluble resins by a soluble polymer such as polyethylene glycol or PEG, made it possible

to go back to experimental procedures familiar to chemistry in solution, whilst preserving simple purification.

However, various problems are associated with the soluble polymer methodology.

For example, the high mass of polymers, e.g., between 2000 and 20,000 daltons, result in a low specific load since a decimolar solution already contains 500 grams of polymer per liter for a PEG with a mass of 5000, which at the most would produce one decimole of expected product per one liter of solution. Such concentrations are used only rarely as they lead to problems of viscosity of the medium.

Another problem associated with soluble polymer methodology is the purification of the products and the recycling of PEGs.

Thus, there existed a long-felt need for new supports for supported organic synthesis which offer both a homogeneous phase and a recyclable salt.

Ionic liquids (Welton et al., 1999; Wasserscheid et al., 2000) have increasingly been used in organic synthesis and in catalysis as they have a certain number of useful and important physicochemical properties, such as high thermal stability, low volatility and very low vapor pressure, low inflammability, and strong solubilization power of the salts, as well as the neutral organic molecules and polymers and ease of recycling.

The claimed invention utilizes ionic liquids as matrices for organic synthesis in a homogeneous phase on soluble support(s),

the soluble support(s) being dissolved in the matrices. The claimed invention confers the advantageous resin-type properties on these ionic liquids without the disadvantageous features, such as reactions in heterogeneous phase on solid support.

Supported synthesis in a homogeneous solution thus satisfies a long felt need of providing the increased reaction efficiency and yields that have not been attained with the heterogeneous systems discussed above.

Moreover, the claimed invention satisfies a long felt need of providing an easily recyclable composition, which simultaneously reduces costs and harmful wastes.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

LEMAIRE Marc



Date 15/07/08

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Professionnel positions and fonctions :

- Assistant Professor CNAM (Paris) 1981-1989.
- Professor 2nd classe (1989), 1^{re} classe (1994) « Exceptional » (2001)
- Director of Masters "Catalysis and physical chemistry " (1991-1998) and “ organic chemistry” (1999-2004)
- Director of UMR 5622 then 5181 (UCBL/CNRS/CPE/INSA) (2001-2007)
- Member of CN CNRS (1993-1998 then 2004-2008) of CN Universities (1998-2004) ; of CA of the French Chemical Society (1998-2003)
- Member of the scientific committees of « Institut de Chimie Séparative de Marcoule » and « Minakem S.A.»

Area of researches :

Organic synthesis, Catalysis, Asymmetric Catalysis, Separation Science and Technology, Molecular Organic Materials, Green Chemistry, Ultra Deep Desulfurization.

Achievements and distinctions :

Author of more than 260 articles and of more than 52 original patents (h Factor = 38)

- Prix Langevin, (Académie des Sciences) 1999
- Médaille Berthelot 1999
- Prix de l'Innovation Rhône-Alpes 2000
- "Invited Editor" (with P. Mangeney) of volume 15 of "Topics in Organometallic Chemistry"
- Prix « Lebel » de la SFC 2007

Exemples of recents articles

1°) Aubry, Sylvain; Razafindrabe, Christian R.; Bourdon, Benjamin; Pellet-Rostaing, Stéphane; Lemaire, Marc. **Synthetic studies towards (±)-phthalascidin 650: Synthesis of a fully functionalized N-protected-α-amino-aldehyde.** Tetrahedron Letters (2007), 48(52), 9163-9166.

2°) Jahjah, Mohamad; Alame, Mohamad; Pellet-Rostaing, Stéphane; Lemaire, Marc. **Catalytic asymmetric hydrogenation of α-ketoesters and quinoline using electronically enriched BINAP.** Tetrahedron: Asymmetry (2007), 18(19), 2305-2312.

3°) Jahjah, Mohamad; Jahjah, Rabi; Pellet-Rostaing, Stéphane; Lemaire, Marc. **Asymmetric hydrogenation of aromatic ketones with new P-chirogenic monophosphine ligands.** Tetrahedron: Asymmetry (2007), 18(10), 1224-1232.

4°) Fournier Dit Chabert, Jérémie; Chatelain, Gregory; Pellet-Rostaing, Stéphane; Bouchu, Denis; Lemaire, Marc.

Benzo[b]thiophene as a template for substituted quinolines and tetrahydroquinolines. Tetrahedron Letters (2006), 47(6),

5°) Berthod, Mikael; Mignani, Gerard; Woodward, Gary; Lemaire, Marc. **Modified BINAP: The How and the Why.** Chemical Reviews (Washington, DC, United States) (2005), 105(5), 1801-1836.

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Ionic Liquids in Synthesis



Second, Completely Revised and Enlarged Edition

Volume 1

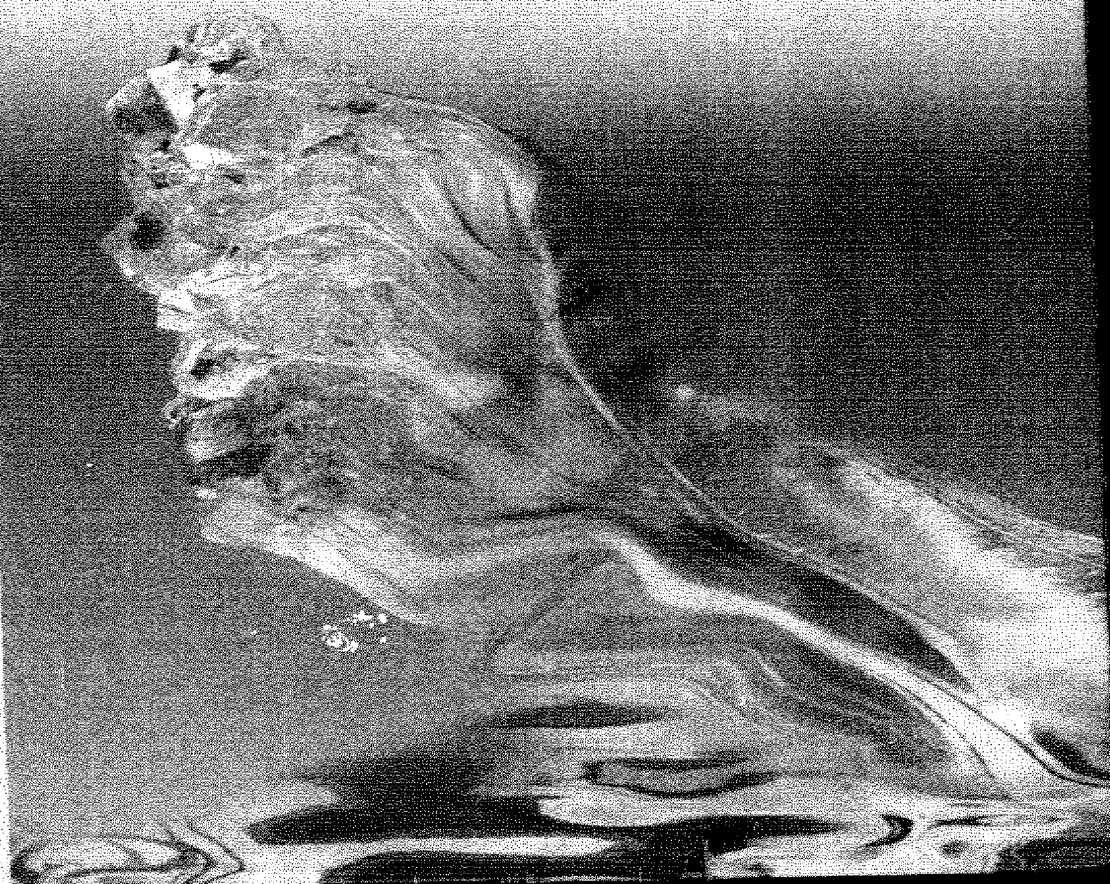


Table 3.1-4 Effect of cation symmetry on melting points of isomeric tetraalkylammonium salts. In each case, the cation (designated $[N_{nmop}]^+$) has four linear-alkyl substituents containing a total of 20 carbons [44]. Salts that are liquid at room temperature are indicated by /

Cation $[N_{nmop}]^+$	Br^-	$[ClO_4]^-$	$[BPh_4]^-$
5555	101.3	117.7	203.3
6554	83.4		
6644	83.0		
8444	67.3		
8543	/	109.5	
6662	46.5		
7733	/	45–58	138.8
8663	/	/	110.2
7731	/	104	
8651	/		
9551	/		
9641	/	/	
11333	67–68	65.5	
11432	/		
8872	62		
9821	/		
13331	71–72	52–53	
9911	/		
10811	/	/	
14222	170	152	
16211	180	155	
17111	210	205	

at examples of salts. The cation radius, r_c , is larger than the anion radius, r_a , in all series of tetraalkylammonium salts in Table 3.1-3. As r_c increases, the melting point decreases. As the alkyl substituents, n , increase, the melting point decreases. As the alkyl chains to 'melt' at room temperature, the polymorphic transition temperature (mp) decreases. As the alkyl chain length increases, the melting point decreases.

up to the symmetry of the cation. The melting points are higher for the symmetric cations than for the asymmetric cations. The melting points are higher for the symmetric cations than for the asymmetric cations. The melting points are higher for the symmetric cations than for the asymmetric cations.

freezing point and melting point. Table 3.1-4 shows the melting points of the cations. The cations that are liquid at room temperature are indicated by /. The cations that are solid at room temperature are indicated by a number.

3.1.3.5 Imidazolium Salts

Changes in the ring substitution patterns can have significant effects on the melting points of imidazolium salts, beyond those anticipated by simple changes in symmetry or H-bonding interactions (i.e., substitution at the C-(2,4,5) positions on an imidazolium ring, affects packing and space-filling of the imidazolium cations). For example, substitution at the C(2)-position of the imidazolium ring increases the melting points of the salts. This is not necessarily an obvious or straightforward result, but may be caused by changes in the cation structure that can induce aromatic stacking or methyl- π interactions between cations. The introduction of other functionalities around the periphery of the ions can also change the interactions between ions. In most cases, additional functions, such as ether groups, increase the number of interactions, and thus increase melting points.

3.1.3.6 Imidazolium Substituent Alkyl Chain Length

The data in Table 3.1-4 illustrate the changes in melting points that can be achieved by changing the symmetry of the cation. [RMI] salts, with asymmetric N -substitution have no rotation or reflection symmetry operations. Changing the alkyl

chain substitution on one of the ring hetero-atoms does not change the symmetry of the cation. However, manipulation of the alkyl chain can produce major changes in the melting points, and on the tendency of the ionic liquids to form glasses rather than crystalline solids on cooling, by changing the efficiency of ion packing.

Characteristic changes in the melting points of organic salts with simple changes in a single alkyl-chain substituent are shown in Fig. 3.1.4 for 1-alkyl-3-methylimidazolium tetrafluoroborate ionic liquids ([RM1M][BF₄]). This highlights the two competing effects on the melting points of changing alkyl-group substituents. It is immediately noticeable, that increasing the substituent length initially reduces the melting point of the IL, with the major trend towards glass formation on cooling for $n = 4-10$. On extending the alkyl chain lengths beyond a certain point (which for alkyl-methylimidazolium salts, is around 8–10 carbons), the melting points of the salts start to increase again with increasing chain length, as van der Waals interactions between the long hydrocarbon chains contribute to local structure by inducing microphase separation between the covalent, hydrophobic alkyl chains and charged ionic regions of the molecules. Initial lengthening of the substituent leads to a reduction in the melting points through destabilization of Coulombic packing, and a trend towards glass formation. However, further increases in substitution lead to increased attractive van der Waals forces between the hydrocarbon chains and increased structural ordering which can be seen with the re-emergence of higher melting points and the formation of structured liquid crystalline materials. The intermediate region (the well in Fig. 3.1.4) represents glass-forming materials in which crystallization is inhibited through the attractive and dispersive terms and the presence of many rotational modes that provide a wide range of ion conformers with similar local energy minima.

A consideration of the changes in molecular structure, and of the underlying effects that this will have in both the liquid and crystal phases helps to rationalize changes in melting points with substitution. The crystalline phases of the IL are dominated by Coulombic ion-ion interactions, comparable to those in typical salt crystals although, since the ions are larger, the Coulombic interactions are weaker (decreasing with n^2). An effect of this is that many organic salts (including 'ionic liquids') crystallize with simple salt-like packing of the anions and cations.

Increased asymmetric substitution on 1-alkyl-3-methylimidazolium salts increases the asymmetric disruption and distortion of the Coulombic packing of ions, leading to substantial decreases in the melting point as the efficiency of packing and crystallization is reduced. This results in (i) melting point reduction and (ii) a pronounced tendency for glass formation on cooling, rather than crystallization, on extending the alkyl substituents. This is indicative of inefficient packing within the crystal structures which is a function of the low-symmetry cations employed. Increasing alkyl chain substitution can also introduce other rheological changes in the ionic liquids including increased viscosity, reduced density, and increased lipophilicity, which must also be considered.

The incorporation of alkyl substituents of increasing chain length in a non-symmetrical arrangement on the ions leads to the introduction of 'bulk' into the crystalline lattice that disrupts the attractive charge-charge lattice. Relatively short



Fig. 3.1.4 Change in true melting point for decreasing increase in n (—) with increasing alkyl chains

space in the sites over gives rise to ordinary prop volume of it

3.1.3.7 Brar (Table 3.1.5) degree of bi melting poi fluorophos reflecting it creases and isomers of

3.1.4 Summary

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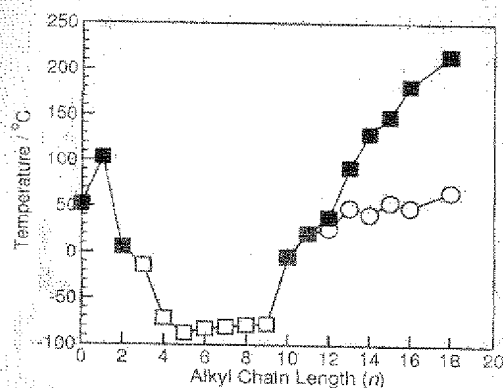


Fig. 3.1.4 Changes in melting points for 1-alkyl-3-methylimidazolium tetrafluoroborate [26] ionic liquids as a function of chain length, showing true melting points (■) and glass transitions (□) with the general trends for decreasing melting points with $n = 1$ to $n = 8$, followed by an increase in melting point and formation of a smectic liquid crystal phase (○) with increasing n clearly visible.

alkyl chains act in this manner, as a buffer, and do not pack well into the available space in the crystalline lattice; high rotational freedom leads to low occupation densities over a relatively large volume of space. This free rotation volume probably gives rise to the 'void-space' considered by Brennecke [48] to explain the extraordinary propensity for sc-CO_2 to dissolve in ILs without substantially changing the volume of the liquid phase.

3.1.3.7 Branching

Table 3.1-5 provides data for a series of ionic liquids, where the only difference is the degree of branching within the alkyl chain at the imidazolium ring 3-position. The melting points and enthalpies for three isomeric 1-butyl-3-methylimidazolium hexafluorophosphate salts, [BMIM][PF₆], increase with the degree of chain branching, reflecting the changes in efficiency of the crystal packing as free-rotation volume decreases and atom density is increased. The same effects are also observed for the two isomers of 1-propyl-3-methylimidazolium hexafluorophosphate, [PMIM][PF₆] [25].

3.1.4

Summary

Liquid structure is defined by short-range ordering, with long-range disorder. The short-range (near-neighbor) structuring of the liquids is a combination of dominant Coulombic charge-charge attractions balanced against the rotational and vibrational freedom of the ions. Changes in the degrees of freedom and increases in